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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/742,512	12/20/2000	Jean-Christophe Audonnet	454313-2541.2	8436

20999 7590 12/12/2003

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	19

DATE MAILED: 12/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/742,512	Applicant(s) AUDONNET ET AL.	
	Examiner Vanessa L. Ford	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *4-17,19,20,22,23,26-29,32,33,37-44 and 46-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 18, 21, 24-25, 30-31, 34-36, 45 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 December 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

FINAL ACTION

1. This Office Action is responsive to Applicant's response filed August 4, 2003 and September 9, 2003 are acknowledged. Claims 1-3,18, 21, 24-25, 30, 35-36, 45 and 56 have been amended.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Objections and Rejections Withdrawn:

3. In view of Applicant's amendment and Response the following Objections are withdrawn:

a) Objection to the specification page 2, paragraph 2.

b) Objection to the specification page 2, paragraph 3.

c) Objection to the specification page 3, paragraph 4.

Rejections Maintained

4. The rejection of claims 1-3, 18, 21, 24-25, 30-31, 34-36, 45 and 56 under 35 U.S.C. 112, first paragraph is maintained for the reasons set forth on pages 3-5, paragraph 5 of the previous Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vaccine comprising a P21 antigen and a Cp15/16 antigen does not reasonably provide

enablement for a vaccine comprising epitopes of a P21 antigen and epitopes of a Cp15/16 antigen.

The claims are drawn to a combination immunological, immunogenic or vaccine composition comprising a first antigen or epitope of interest from a first enteric pathogen comprising *Cryptosporidium* and/or a first vector that expresses the first antigen or epitope of interest, and a second antigen or epitope of interest from a second enteric pathogen and/or the first vector that expresses the first antigen or epitope of interest also expresses the second antigen or epitope of interest and a pharmaceutically acceptable vehicle when the first and second enteric pathogens can be the same enteric pathogen or different enteric pathogens and a kit comprising the combination composition and optionally comprising instructions for admixtures and/or administration.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification teaches that P21 (page 14) and Cp15/16 (page 14) are to be included in the claimed immunogenic composition or vaccine. The specification is enabling only for the claims limited to the P21 antigen and the Cp15/16 antigen as disclosed in the specification. The specification is not enabling for the epitopes of P21 and Cp15/16. The specification mentions that polypeptides which can be used in the practice of the instant invention have at least 75% homology or identity to the P21 antigen or the Cp15/16 antigen (pages 15-16). The specification states that one skilled in the art could make and use polypeptides that are at least 75% homologous or identical to the P21 and Cp15/16 antigen. The specification does not disclose <u>any specific</u> structural information about the epitopes or fragments of the P21 or Cp15/16 antigens. The specification does not disclose, What amino acids are involved in these epitopes or fragments? What amino acid substitutions or deletions can be made in the polypeptide so that the polypeptide retains the same activity as the P21 and Cp15/16 antigens? One skilled in the art would require guidance in order to make or use the epitopes or fragments of the above recited *Cryptosporidium parvum* antigens in a manner reasonable in correlation within the scope of the claims.

Factors to be considered in determining whether undue experimentation is required, are set forth in <u>In re Wands</u> 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification regarding how to make and use epitopes or fragments of the P21 and Cp15/16 antigen, and 3) the relative skill of those in the art is commonly recognized as quite high (post - doctoral level).

In view of all of the above, it is determined that it would require undue experimentation to make and use epitopes or fragments of the P21 and Cp15/16 antigens in commensurate in scope with the claims. Because of lack of guidance provided in the specification, it is determined that the specification is not enabled for an immunogenic composition or vaccine that comprises epitopes or fragments of the P21 and Cp15/16 antigens.

Applicant urges that that the claimed invention is clearly enabled because the skilled artisan would readily understand that standard techniques for identifying epitopes can be used to characterize epitopes of P21 and Cp 15/16. Applicant urges that predictability in the art did exist at the time of filing and coupled with the knowledge of one skilled in the art and the guidance of the present application, there is sufficient evidence that Applicant' disclosure does satisfy the enablement requirement. Applicant refers to the teachings of Geysen et al, Hoop, Van Regenmortel and Pelleque to support the position that techniques of identifying epitopes are known in the art. Applicant urges that no undue experimentation would be necessary, sufficient direction and guidance are presented in the specification and the relative skill of those skilled in the art is high, such that the claims are sufficiently enabled for a vaccine comprising epitopes of a P21 antigen and epitopes of a Cp 15/16 antigen.

Applicant's arguments filed August 4, 2003 and September 9, 2003 have been fully considered but they are not persuasive. The claims as amended encompass isolated polypeptides that are variants of the P21 antigen and the Cp 15/16 antigen. The specification does not provide enablement for the full scope of the claimed invention. Applicant has provided no structural description accompanying the variants encompassed by the claims. While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple

modifications of other types and the positions within the polypeptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining particular (claimed) activity are limited in any polypeptide and the result of such modifications is unpredictable. One skilled in the art would not expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some polypeptide is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such nucleic acid polypeptides. Applicant has cited prior art (i.e. Geysen et al, Hoop, Van Regenmortel and Pelleque) teaches that techniques are available screening for epitopes. However, 35 U.S.C. 112, first paragraph requires that the applicant teach how to make and use the claimed epitopes used in the composition and not how to "find" epitopes that would be encompassed by the claimed invention. One skilled in the art would require guidance in order to make and use the claimed isolated polypeptide commensurate in scope with the claims. Therefore, Applicant is not enabled for the claimed invention.

5. The rejection of claims 1-3, 18, 21, 24-25, 30-31, 34-36, 45 and 56 as unpatentable over Perryman et al *(WO 98/07320, published February 26, 1998)* in view of Jenkins et al (*U.S. Patent No. 5,591, 434, published January 7, 1997)* is maintained for the reasons set forth on pages 6-8, paragraph 7 of the previous Office Action.

The rejection was on the grounds that Perryman et al teach a vaccine formulation that comprises recombinant C7 protein from *Cryptosporidium parvum* (SEQ ID NO: 12, which is P21) in monophosphoryl lipid A trehalose dimycolate adjuvant (pages 25-26). Perryman et al teach the use of recombinant proteins and synthetic peptides containing *Cryptosporidium parvum* epitopes for inducing an antigenic response in animals (see the Abstract). Perryman et al teach that the vaccine formulations comprising the

antigens of the invention can be prepared for both human and veterinary treatments. Perryman et al teach that the vaccine formulations comprise appropriate antigen and a pharmaceutically acceptable carrier (page 11). Perryman et al also teach that the vaccine formulations of the invention may comprise a suitable adjuvant such as aluminum hydroxide or aluminum phosphate and further comprise stabilizers such as carbohydrates or glucose (page 12). Perryman et al teach that the vaccine formulations may include combinations of appropriate antigens (page 11).

Perryman et al do not teach the use of the Cp15/16 antigen of *Crytosporidium parvum.*

Jenkins et al teach the use of Cp15/16 recombinant proteins which are effective in the immunization of animals against cryptosporidiosis (columns 2, lines 6-9). Jenkins et al teach that Cp15/16 proteins are preferred in the treatment of bovine and are administered in the presence of a physiologically acceptable diluent (column 7, lines 59-67). Jenkins et al teach that the Cp15/16 protein compositions may also include vaccine stabilizers and adjuvants (column 8, lines 1-8). It is well known in the art to package each antigen used in the claimed invention in separate containers, package them together in a kit which includes instructions for preparing admixtures and instructions for administering the claimed composition.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the Cp15/16 vaccine composition of Jenkins et al to the vaccine formulations of Perryman et al because Perryman et al teach that the vaccine formulations may include combinations of appropriate antigens (page 11). It would be expected barring evidence to the contrary that a vaccine comprising both the P21 antigen and the Cp15/16 antigen would be effective against cryptosporidiosis because Jenkins et al teach that Cp15/16 proteins are effective for immunization of a variety of animals against *Cryptosporidium parvum*, particularly for the production of hyperimmune colostrums that may be used to confer passive immunity against the parasite in young or immunodeficient animals (column 8, lines 14-22) and Perryman et al demonstrates that immunization of adult cows with P21 gave high titers of antibodies to the P21 antigen and to the native P23 antigen (page 26). Perryman et al also demonstrated that colostrums collected from immunized cows also gave high titers of antibodies to P21 and the native P23 (page 26) and Perryman et al suggest that the antibodies may impart passive immunity to *Cryptosporidium parvum* in an animal subject in need thereof (page 11).

Applicant urges that the two cited documents do not render the instant invention. Applicant urges that incentive or motivation is required for modifying the reference teachings. Applicant urges that both suggestion of the claimed invention and the expectation of success must be founded in the prior art and not in Applicant's

disclosure. Applicant urges that one of skill in the art reading Perryman et al and Jenkins et al would not have been motivated to combine Cp15/10 and P21. Applicant urges that neither Perryman et al nor Jenkins et al provide any teachings or guidance regarding such combination. Applicant urges that neither Perryman et al nor Jenkins et al provide any expectation of success resulting from the combination especially in view of efficacy interference a phenomenon any individual skilled in the art would be aware of.

Applicant's arguments filed August 4, 2003 and September 9, 2003 have been fully considered but they are not persuasive. The claims are drawn to a combination immunological, immunogenic or vaccine composition consisting essentially of a first antigen or epitope of interest from a first enteric pathogen comprising *Cryptosporidium* and/or a first vector that expresses the first antigen or epitope of interest, and a second antigen or epitope of interest from a second enteric pathogen and/or the first vector that expresses the first antigen or epitope of interest also expresses the second antigen or epitope of interest and a pharmaceutically acceptable vehicle when the first and second enteric pathogens can be the same enteric pathogen or different enteric pathogens and a kit comprising the combination composition and optionally comprising instructions for admixtures and/or administration. Perryman et al teach a vaccine formulation that comprises recombinant C7 protein from *Cryptosporidium parvum* (SEQ ID NO: 12, which is P21) in monophosphoryl lipid A trehalose dimycolate adjuvant (pages 25-26). Perryman et al do not teach the use of the Cp15/16 antigen of *Crytosporidium parvum*. However, Jenkins et al teach the use of Cp15/16 recombinant proteins which are

effective in the immunization of animals against cryptosporidiosis (columns 2, lines 6-9). Therefore, it would have been obvious to combine the P21 as taught by Perryman et al with the of Cp15/16 recombinant proteins as taught by Jenkins et al because Jenkins et al teach that Cp15/16 proteins are effective for immunization of a variety of animals against *Cryptosporidium parvum*, particularly for the production of hyperimmune colostrums that may be used to confer passive immunity against the parasite in young or immunodeficient animals (column 8, lines 14-22) and Perryman et al demonstrates that immunization of adult cows with P21 gave high titers of antibodies to the P21 antigen and to the native P23 antigen (page 26). One of skill in the art would have further been motivated to combine the teachings of cited references because Perryman et al discloses that cryptosporidiosis has emerged as an important enteric disease of humans and animals (page 1) and Jenkins et al discloses that the young and immunosuppressed are particularly at risks in regards to infections caused by *Cryptosporidium parvum*. One of skill in the art would reasonably expect that a composition comprising an antigen (i.e. P21) that is effective in treating adult as well as an antigen (i.e. Cp 15/16) that is effective in treating young or immunodeficient individuals would provide better protection against *Cryptosporidium parvum* infections. It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is used for the same purpose. The idea of combining them flows logically from their having been individually taught in the art; thus claims that require no more than mixing together of two conventional spray-dried detergents set forth *prima facie* obvious

subject matter. See In re Kerkhoven No. 79-586, 205PQ 1069, May 15, 1980. It should be noted that Perryman et al teaches the use of P21 combined with other "appropriate" antigen. One of skill in the art would recognize "appropriate" antigens to be defined as antigens that protect from pathogens such as *Cryptosporidium parvum* or other organisms that may be pathogenic to the subject in which it is administered and that does not cause efficacy interference when co-administered. Applicant appears to be arguing limitations that are not in the claims with their comments regarding "efficacy interference". One in the art could reasonably conclude that no efficacy interference would exist when administering a composition comprising both P21 and Cp 15/15 because ~~the~~ Jenkins et al suggests that composition can be administered to young and immunodeficient animals to confer passive immunity against cryptosporidiosis and also adult subjects. Perryman et al teach that adult subjects can be immunized with P21. It should be noted that the instant specification teaches that the limitations of efficacy interference are ~~meet~~ met with the ability of the claimed composition to be administered to pregnant (adult) as well as young or new born animals (pages 5-6).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re*

Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). There is nothing on the record to show that the combination of teachings would not suggest the claimed invention.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
December 9, 2003

NITA MINNIFIELD
PRIMARY EXAMINER
12/10/03